

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

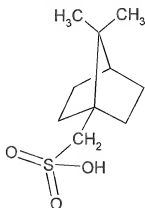
| | | |
|-------------|----------------------------------|---|
| Appln. Of: | GEORGE KRSEK |) |
| Serial No.: | 10/772,675 |) |
| Filed: | February 4, 2004 |) |
| For: | METHOD TO SEPARATE STEREOISOMERS |) |
| Group: | 1723 |) |
| Examiner: | DRODGE, JOSEPH |) |
| | DOCKET: |) |
| | KONEC 04.01 |) |

Commissioner of Patents & Trademarks
Washington, D.C. 20231

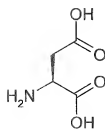
DECLARATION UNDER 37 CFR 1.132

I, GEORGE R. KRSEK, Ph.D., hereby declare:

1. I am an Applicant in the above-referenced Application.
2. I prepared and/or purchased a variety of optically active acids, and attempted to use each of those optically active acids to resolve dl-methylphenidate.
3. Between July 9, 2001 and July 23, 2001, I unsuccessfully attempted to resolve dl-threo-methylphenidate using d-10-camphor sulfonic acid, compound I,

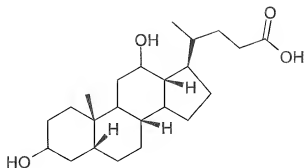


L-aspartic acid, compound II,



II

Deoxycholic acid, compound III



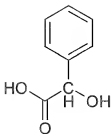
III

D-pyrrolidine carboxylic acid, compound IV,



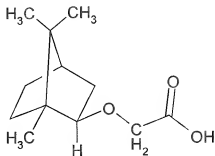
IV

and (+) Mandelic acid, compound V



V

4. On September 10, 2001, I attempted without success to resolve dl-threo-methylphenidate using (-) borneoloxoacetic acid, compound VI



VI

5. Attachment "A" hereto recites data relating to the synthetic yield reported by Leffler and Calkins ("Leffler") for the preparation of *l*-menthoxyacetic acid from *l*-menthol, and data reported in the Application on Page 9 / Line 16 through Page 10 / Line 20 for my preparation of *l*-fenchyloxyacetic acid from *l*-fenchyl alcohol.

6. Attachment "B" hereto comprises true and accurate copies of Page 1188 and Page 1513 of the 2005-2006 Aldrich Catalog ("Aldrich").

7. Aldrich at Page 1188 recites a price for optically *l*-fenchyl alcohol of \$62.90 for 500 grams. See, Attachment "B" at Page 1188 - Product No. 196444-500G.

8. Aldrich at Page 1513 recites a price for *l*-menthol of \$94.50 for 500 grams. See, Attachment "B" at Page 1513 - Product No. M2780-500G-A.

9. Leffler reports a yield of 78-84% for the synthesis of *l*-menthoxyacetic acid from *l*-menthol. See, Leffler at Page 2.

10. I prepared 90 grams, or 0.48 moles, of *l*-fenchyloxyacetic acid using 200 grams, or 1.30 moles, of *l*-fenchyl alcohol for a yield of 36.90%. See, Application at Page 9 / Line 16 through Page 10 / Line 20.

11. Using the yield reported by Leffler and starting with 500 grams of *l*-menthol would give 475 grams of *l*-menthoxyacetic acid.

12. The price of *l*-menthoxyacetic acid produced, based on the cost of the starting *l*-menthol, would be \$0.20 per gram.

13. Using the method of Example 4 of the Application and starting with 500 grams of *l*-fenchyl alcohol would give 225 grams of *l*-fenchyloxyacetic acid.

14. The price of *l*-fenchyloxyacetic acid produced, based on the cost of the starting *l*-fenchyl alcohol, would be \$0.28 per gram.

15. The undersigned declares further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code.


GEORGE R. KRSEK, Ph.D.

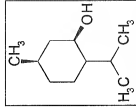
Date: 1 Nov 06

CERTIFICATE OF ELECTRONIC FILING

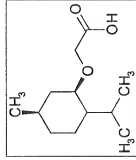
I hereby certify that on this 2nd day of November, 2006, the Declaration Under 37 CFR 1.132 is being filed via the Web Enabled Patent Filing System (EFT-WEB).

By:  _____

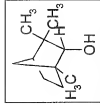
ATTACHMENT “A”



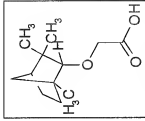
MENTHYL ALCOHOL
MOL. WT. = 156 g/mole



MENTHOXYACETIC ACID
MOL. WT. = 190 g/mole



FENCHYL ALCOHOL
MOL. WT. = 154 g/mole



FENCHOXYACETIC ACID
MOL. WT = 188 g/mole

| STARTING ALCOHOL | PRICE FOR 500 G STARTING ALCOHOL | YIELD FOR OPTICALLY ACTIVE OXYACETIC ACID FROM STARTING ALCOHOL | YIELD IN GRAMS OF OPTICALLY ACTIVE OXYACETIC ACID STARTING WITH 500 G. ALCOHOL | PRICE PER GRAM BASED ON STARTING ALCOHOL |
|------------------|----------------------------------|---|--|--|
| MENTHOL | \$94.50 | 78% | 475 grams | \$0.20 |
| FENCHYL ALCOHOL | \$62.90 | 36.80% | 225 grams | \$0.28 |

ATTACHMENT “B”

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Aldrich

Advancing Science

2005-2006
U.S.

Aldrich

Fat Browne RR
 (-)-Fenchone, 98%
 [6416-57-5] C₁₀H₁₆O FW 262.31
 dye content 95%
 mp 147 to 158 °C
 R 3937/38 S 26-36 RTECS# ST2500000 TSCA
 236039-25G glass btl 25 g 31.00

Fatty acid methyl esters/C₆-C₂₂ straight-chain, kit containing 19 standards
 25,222-0 Methyl arachidate 1g
 85,527-8 Methyl behenate 500mg
 25,994-2 Methyl caproate 2.5mL
 26,067-3 Methyl caprylate 2.5g
 29,903-0 Methyl decanoate 2.5g
 14,900-4 Methyl erianthate 2.5mL
 28,607-9 Methyl heptadecanoate 250mg
 29,904-9 Methyl heneicosanoate 100mg
 23,459-1 Methyl laurate 2.5g
 14,898-9 Methyl myristate 2.5g
 28,603-4 Methyl nonadecanoate 500mg
 24,589-5 Methyl nonanoate 2.5g
 26,065-7 Methyl palmitate 1g
 23,545-8 Methyl pentadecanoate 2.5g
 M8,070-9 Methyl stearate 1g
 29,905-7 Methyl tetraacosanoate 100mg
 28,734-2 Methyl tricosanoate 100mg
 M8,540-9 Methyl tridecanoate 2.5g
 29,941-3 Methyl undecanoate 2.5g
 299022-1KT 1 kit 400.80

Fatty acids/C₆-C₂₂ straight-chain, kit containing 19 standards
 E23-1 Arachidic acid
 21,694-1 Behenic acid
 15,376-1 Decanoic acid
 15,378-8 Dodecanoic acid
 21,965-5 Heneicosanoic acid
 H100-0 Heptadecanoic acid
 25,873-3 Heptanoic acid
 15,374-5 Hexanoic acid
 15,379-6 Myristic acid
 M5252 Nonadecanoic acid
 N2,990-2 Nonanoic acid
 15,375-3 Octanoic acid
 25,872-5 Palmitic acid
 P260-0 Pentadecanoic acid
 26,830-0 Stearic acid
 23,468-0 Tetraacosanoic acid
 21,859-6 Tricosanoic acid
 T0502 Tridecanoic acid
 17,147-6 Undecanoic acid
 R 34 S 26-28-36/37/39-45
 298514-1KT 1 kit 286.20

Fenbutenol, 96%
 [36330-85-5] C₁₂H₂₄O₂ FW 254.28
 Merck 13,3990
 mp 184 to 187 °C
 R 25 S 28-45 RTECS# DV1761000

538515-1G glass btl 1 g 21.90
 538515-5G glass btl 5 g 72.90

(-)-Fenchone, 98%
 (-)-Fenchone, (-)-1,3,3-trimethyl-2-norbornanone
 [7787-20-4] C₁₀H₁₆O FW 152.23
 [α]_D²⁰ -50.5°, neat
 Beil 7,IV,212; Fieser 8,228
 bp 192-194 °C
 density 0.948 g/mL 25 °C
 mp 5 to 6 °C
 n_D²⁰ 1.461
 R 10 S 23-24/25; TSCA Fp 52°C (128°)
 196436-50G glass btl 50 g 23.30
 196436-250G glass btl 250 g 73.30



(+)-Fenchone, 98.0% (GC, sum of enantiomers)
 (1S)-1,3,3-Trimethylbicyclo[2.2.1]heptan-2-one, (+)-1,3,3-trimethyl-2-norbornanone
 [5695-62-9] C₁₀H₁₆O FW 152.23
parum
 [α]_D²⁰ +60±3°, neat
 Merck 13,3995; Beil 7,IV,212
 bp 63-65 °C/13 mm Hg mp 5 to 7 °C
 density 0.945 g/mL 20 °C
 mp 5 to 7 °C n_D²⁰ 1.463
 S 23-24/25 RTECS# R8787500 Fp 66°C (151°)
 46210-100ML-F 100 mL 115.10

(-)-endo-(+)-Fenchyl alcohol, 96%
 (+)-Fenchol
 [2217-02-9] C₁₀H₁₈O FW 154.25
 Beil 6,IV,278
 mp 39 to 45 °C
 S 22-24/25 Fp 14°C (165°)



196444-5G glass btl 5 g 18.90
 196444-100G glass btl 100 g 20.30
 196444-500G glass btl 500 g 62.90

B-Fenoxoprop ethyl, see Ethyl (2S,4S)-2-(4-hydroxybenzoate-2-ylmethyl)phenylpropanoate Page 1128
Ferene[®], see 3 (2-Hydroxy-5,6-bis(sulfo-2-4-lynyl)-2,4-tiazine diadium salt Page 2054
Ferric ammonium citrate, see Ammonium iron(III) citrate Page 224

Ferric citrate
 [3522-50-7] Fe₂(C₆H₅O₇)₂ FW 244.94
 Fe 16.5-18.5%
 light sensitive
 F6129-250G 250 g 30.60
 F6129-1KG 1 kg 100.30

Ferric hydroxide oxide
 [20344-49-4] Fe(OH)₃ FW 88.85
 Merck 13,4055
 TSCA

crystalline powder, 50-80 mesh
 546267-50G poly btl 50 g 45.70
 546267-250G poly btl 250 g 170.00

catalyst grade, 30-50 mesh
 371254-50G poly btl 50 g 47.00
 371254-250G poly btl 250 g 178.50

ferrocene
 [102-54-5]
 Merck 13,40
 bp
 mp
 R 11
 F408-5G
 F408-100G
 F408-500G
Ferrocenone
 [1287-16-7]
 Beil 16,IV,11
 mp

335045-5X

ferrocene
 [13716-91-2]
 Beil 16,IV,11
 mp
 R 2021

335053-1G

335053-5G

ferrocene
 [12152-94-2]
 Contains var
 mp
 R 3637

455547-5G
 455547-25G

Ferrocenone

[12093-10-6]
 Beil 16,IV,11
 mp

S 23-24/25

122459-5G

122459-5G

122459-25G

Ferrocenone

[1271-42-7]
 Beil 16,IV,11
 mp

106887-1G

106887-10G

Ferrocene

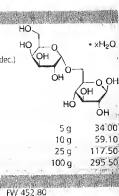
C₁₂H₁₀Fe₂O₂

S 22-24/25

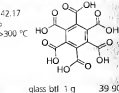
US \$

US \$

■ Menthylace ■



92 to 94 °C
glass btl 100 mg 37.10
glass btl 1 g 264.50



glass btl 1 g 39.90

to 300 °C. Kit containing 24

34-136°C
280°C
120°C
198-200°C
dinitrophenylhydrazine 159-
methylethanol 70-73°C
40-241°C
ene 59-61°C
id 209-210°C

9-262°C
86°C
70-172°C
glutaric acid 180-181°C
13°C
benzoic acid 219-220°C
150-152°C

1 kit 290.40

34-136°C
280°C
120°C
198-200°C
dinitrophenylhydrazine 159-
methylethanol 70-73°C
40-241°C
ene 59-61°C
id 209-210°C

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glutaric acid 180-181°C
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280°C
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dinitrophenylhydrazine 159-
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86°C
70-172°C
glutaric acid 180-181°C
13°C
benzoic acid 219-220°C
150-152°C

1 kit 290.40

34-136°C
280°C
120°C
198-200°C
dinitrophenylhydrazine 159-
methylethanol 70-73°C
40-241°C
ene 59-61°C
id 209-210°C

9-262°C
86°C
70-172°C
glutaric acid 180-181°C
13°C
benzoic acid 219-220°C
150-152°C

1 kit 290.40

trans-β-Menthyl-ene-2,8-diol, 99%
[42370-41-2] C₁₀H₁₈O₂ FW 170.25
Beil 6,752
bp 270-271 °C
mp 130 to 132 °C
RTECS# F1200000

247774-10G glass btl 10 g 29.70
247774-50G glass btl 50 g 91.60

(±)-Menthyl-ene-2,8-diol, mixture of isomers, 97%
[18479-60-0] C₁₀H₁₈O FW 154.25
(R,R)-isomer -67%, (S,S)-isomer -33%
[α]_D²⁰ +99°, c = 4.2 in C₆H₆:CH₃
bp 115-116 °C/10 mm Hg
density 0.941 g/mL 25 °C
n_D²⁰ 1.486
TSCA Fp 103°C (218°F)

183741-10G glass btl 1 g 26.10
183741-10G glass btl 10 g 155.50

(R)-Menthyl-ene-2,8-diol, 99% (GLC)
[9-36-Dimethyl-4,5,6,7-tetrahydrobenzofuran
[17957-94-7] C₁₀H₁₈O FW 150.22
technical
[α]_D²⁰ +97.55°, neat
Beil 17,1,516
bp 204-206 °C density 0.97 g/mL 20 °C
[57594-25]ML-F 25 mL 96.70

Menthol, 99%
[89-78-1] C₁₀H₁₈O FW 156.27
Beil 13,5861; Beil 6,IV,151; Fieser 13,172
bp 216 °C mp 34 to 36 °C
density 0.89 g/mL 25 °C vp 0.8 mm Hg (20 °C)
R 37/38-41 S 26-36 RTECS# OT0350000 Fp 93°C (200°F)

M2772-5G-A glass btl 5 g 21.00
M2772-100G-A glass btl 100 g 23.50
M2772-500G-A glass btl 500 g 78.20

Menthol solution

NMR reference standard, 30 wt. % in chloroform-d (99.8
atom % D)
API & Dept demonstration
R 22-38-40-41-48/2022 S 36/37/39 Hygroscopic
551376-1EA 5mm x Bin. 1 ea 116.00

LC-NMR reference standard, 50% in chloroform-d (99.9
atom % D), chromium(III) acetylacetonate 0.5%
R 22-38-40-41-48/2022 S 36/37/39 Hygroscopic, light sensitive
513290-1EA 5mm x Bin. 1 ea 318.00

(R)-2,5-Dimethyl-2-menthyl-3-pentanol, 98%
[2216-51-5] C₁₃H₂₄O FW 156.27
Beil 6,IV,150; Fieser 12,294, 13,172, 16,203
bp 212 °C
density 0.89 g/mL 25 °C
mp 41-44 °C
bp 42 to 45 °C
density 0.8 mm Hg (20 °C)
R 37/38-41 S 26-39 RTECS# O1070000 Fp 101°C (214°F)

99%
[α]_D²⁰ -50°, c = 10 in C₂H₅OH
ee 99% (GLC)

M2780-25G-A poly btl 25 g 14.30
M2780-100G-A poly btl 100 g 29.20
M2780-500G-A poly btl 500 g 94.50

≥99%, sublimed
[α]_D²⁰ -50°, c = 10 in C₂H₅CH₃OH
TSCA

588733-1G glass btl 1 g 34.50

(1S,2R,5S)-(+)-Menthol, 99%

(+)-Menthol
[15356-60-2] C₁₀H₁₈O FW 156.27
[α]_D²⁰ +48°, c = 10 in C₂H₅OH
ee 96% (GLC)
Beil 6,IV,151; Fieser 12,294, 13,172
bp 103-104 °C/9 mm Hg vp 0.8 mm Hg (20 °C)
mp 43 to 44 °C
R 37/38-41 S 26-36 RTECS# Q7070000, ISCA
Fp 101°C (214°F)

224464-10G glass btl 10 g 33.30
224464-50G glass btl 50 g 110.50

(-)-Menthone, 90%

[14073-97-3] C₁₀H₁₈O FW 154.25
[α]_D²⁰ -20°, neat
Merck 13,5862; Beil 7,IV,87; Fieser 14,201;
16,204
bp 207-210 °C
density 0.893 g/mL 25 °C
vp 0.5 mm Hg (20 °C)
n_D²⁰ 1.45
Isomeric menthone
S 39-42/25 TSCA Fp 72°C (162°F)

218235-25G glass btl 25 g 23.60
218235-100G glass btl 100 g 54.00

(-)-Menthylacetyl chloride, 97%

[17356-62-4] C₁₂H₂₀ClO₂
FW 232.75
[α]_D²⁰ -10°, neat
density 1.033 g/mL 25 °C
n_D²⁰ 1.469
R 34 S 26-27-36/37/38-45
Fp 113°C (235°F)

453714-1G glass btl 1 g 23.90
453714-5G glass btl 5 g 79.80

Menthyl acetate, 97%

(R)-4-ethyl-5-methyl-2-methylpentanoate, 98%
[135863-5] C₁₃H₂₆O₂ FW 198.30
FW 232.75
bp 228-229 °C
density 0.922 g/mL 25 °C
TSCA Fp 92°C (198°F)

422770-25ML glass btl 25 mL 21.90
422770-100ML glass btl 100 mL 60.70

(R)-(-)-Menthyl acetate, 98%

[12623-23-6] C₁₃H₂₆O₂ FW 198.30
[α]_D²⁰ -81°, c = 8 in C₆H₆
ee 98% (GLC)
Beil 6,IV,153
bp 229-230 °C
density 0.92 g/mL 25 °C
RTECS# A690000, TSCA Fp 77°C (171°F)

441058-25ML glass btl 25 mL 24.60
441058-100ML glass btl 100 mL 65.60